Biochemical Pharmacology 82 (2011) 1335–1351

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2, an electrophilic lipid mediator of anti-inflammatory and pro-resolving signaling

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ARTICLE INFO

Article history:
Received 9 June 2011
Accepted 29 July 2011
Available online 6 August 2011

Keywords:
15-deoxy-$\Delta^{12,14}$-prostagandin J_2
Cyclopentenone prostaglandin
Inflammation
Resolution
Anti-inflammation

ABSTRACT

15-deoxy-$\Delta^{12,14}$-prostagandin J_2 (15d-PGJ2) is produced in the inflamed cells and tissues as a consequence of upregulation of cyclooxygenase-2 (COX-2). 15d-PGJ2 is known to be the endogenous ligand of peroxisome proliferator-activated receptor gamma (PPARγ) with multiple physiological properties. Though one of the terminal products of the COX-2-catalyzed reactions, this cyclopentenone prostaglandin exerts potent anti-inflammatory actions, in part, by antagonizing the activities of pro-inflammatory transcription factors, such as NF-κB, STAT3, and AP-1, while stimulating the anti-inflammatory transcription factor Nrf2. These effects are not necessarily dependent on its activation of PPARγ, but often involves direct interaction with the above signaling molecules and their regulators. The locally produced 15d-PGJ2 is also involved in the resolution of inflammatory responses. Thus, 15d-PGJ2, especially formed during the late phase of inflammation, might inhibit cytokine secretion and other events by antigen-presenting cells like dendritic cells or macrophages. 15d-PGJ2 can also affect the priming and effector functions of T lymphocytes and induce their apoptotic cell death. These represent a negative feedback explaining how once-initiated immunologic and inflammatory responses are switched off and terminated. In this context, 15d-PGJ2 and its synthetic derivatives have therapeutic potential for the treatment of inflammatory disorders.

Contents

Abbreviations: 15d-PGJ2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2; COX-2, cyclooxygenase-2; PPARγ, proliferator-activated receptor gamma; PGH2, prostaglandin H_2; PGD2, prostaglandin D_2; PGJ2, prostaglandin J_2; NF-κB, nuclear factor-kappaB; STAT3, signal transducers and activators of transcription 3; Nrf2, nuclear factor-erythroid 2p45 (NF-E2)-related factor; AP-1, activator protein-1; GSH, reduced glutathione; CNS, central nervous system; PGE2, prostaglandin E_2; MMP, matrix metalloproteinases; TNF-α, tumor necrosis factor-alpha; iNOS, inducible nitric oxide synthase; NO, nitric oxide; HO-1, heme oxygenase-1; I/R, ischemia/reperfusion; LPS, lipopolysaccharide; EAE, encephalomyelitis; COPD, chronic obstructive pulmonary disease; IFN-γ, interferon-γ; MPO, myeloperoxidase; PGA1, prostaglandin A_1; ICAM-1, intercellular adhesion molecule-1; MCP-1, macrophage chemotactic protein 1; α-SMA, α-smooth muscle actin; IL, interleukine; HAT, histone acetyltransferase; HDAC, histone deacetylase; NAC, *N*-acetylcysteine; PGA2, prostaglandin A_2; BSO, buthionine sulfoximine; IκBα, inhibitory protein κB; IKK, IκB kinase; JNK, c-Jun N-terminals kinase; MAPK, mitogen activated protein kinase; TF, tissue factor; ERK, extracellular-regulated protein kinase; MEKK1, MAPK kinase; mPGES, microsomal prostaglandin E synthase; TLR, toll-like receptor; ox-LDL, oxidized low-density lipoprotein; HUVECs, human vascular endothelial cells; HMEC-1, human microvascular endothelial cell line; SOCS, suppressor of cytokine signaling; JAK, Janus kinase; TGF, transforming growth factor; EGF, epidermal growth factor; ES, embryonic stem; LIF, leukemia inhibitory factor; NQO1, NAD(P)H:quinone oxidoreductase-1; Keap1, Kelch-like erythroid cell-derived protein with 'capn'collar homology associated protein; ARE, antioxidant response elements; EpRE, electrophile response element; VSMCs, vascular smooth muscle cells; CO, carbon monoxide; SIN-1, 3-morpholinosydnonimine hydrochloride; GCL, glutamate cysteine ligase; PMNs, polymorphonuclear leukocytes; HSA, human serum albumin.

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doi:10.1016/j.bcp.2011.07.100

1. Introduction

15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ2), a cyclopentenone-type prostaglandin with a wide spectrum of physiological activities, is one of the terminal products of the cyclooxygenase-2 (COX-2) pathway. 15d-PGJ2 was initially discovered as a potent ligand for peroxisome proliferator-activated receptor gamma (PPARγ), a member of the nuclear receptor superfamily and a ligand-activated transcription factor with pleiotropic effects on adipocyte differentiation, glucose homeostasis, lipid metabolism, growth, and inflammation. 15d-PGJ2 differs from other prostaglandins, both chemically and biologically, in several respects [1]. Though one of the major prostaglandins formed by COX-2 activity, 15d-PGJ2 has anti-inflammatory, anti-proliferative and cytoprotective effects. 15d-PGJ2 is produced abundantly in inflamed sites, and its potential role in protecting cells and tissues from acute inflammation, especially by facilitating the resolution of inflammation, has been suggested [1–3]. This review is intended to provide a comprehensive overview of the anti-inflammatory and pro-resolving potential of 15d-PGJ2 and to propose underlying molecular mechanisms.

2. Formation and structural characteristics of 15d-PGJ2

The rate-limiting step in the prostaglandin biosynthesis is the COX-catalyzed conversion of arachidonic acid mobilized from the membrane phospholipid to prostaglandin H_2 (PGH2). PGH2 is metabolized to a series of physiologically important prostanoids and thromboxanes by specific enzymes. An enzyme prostaglandin D_2 (PGD2) synthase catalyzes the conversion of PGH2 to PGD2 (Fig. 1).

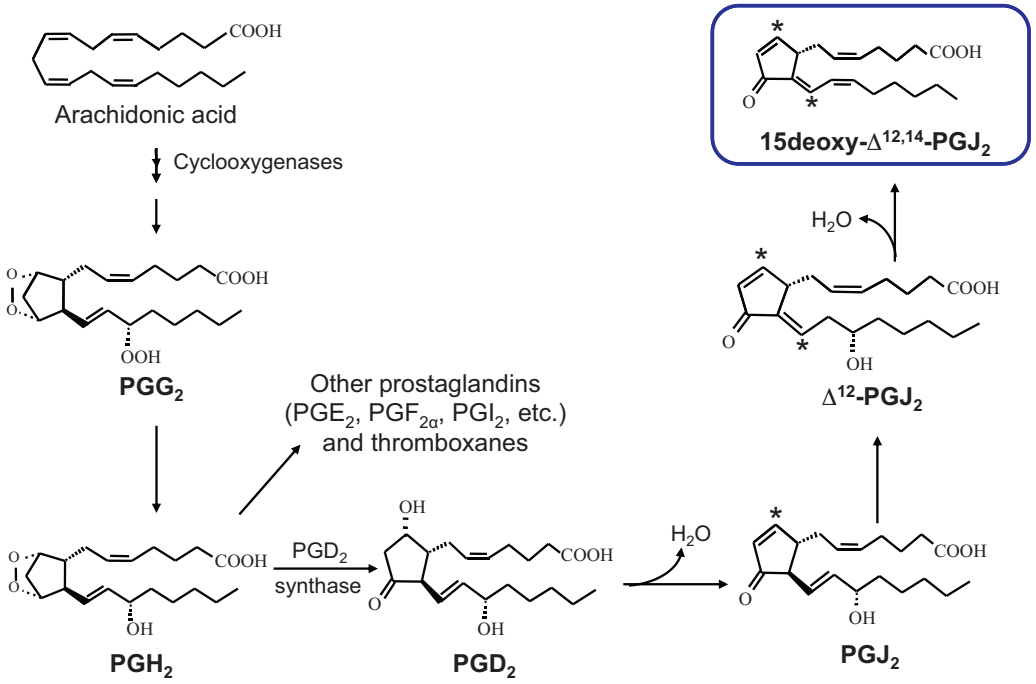

Fig. 1. Formation of 15d-PGJ2 in the arachidonic acid cascade. 15d-PGJ2 and its precursor cyclpentenone prostaglandins have electrophilic carbon(s) designated as asterisk, due to the α,β-unsaturated carbonyl moiety.

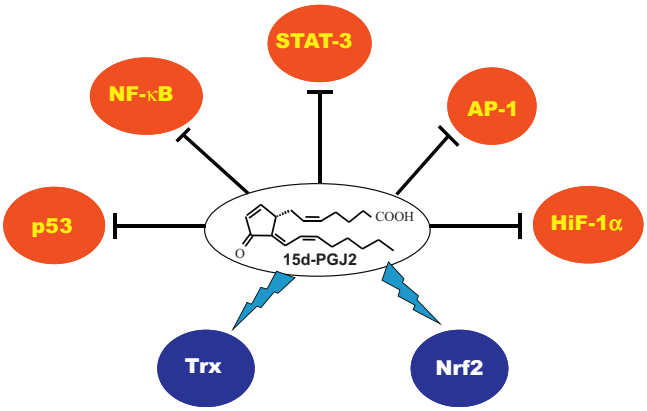

Fig. 2. Modulation of various redox regulators by 15-PGJ2.

15d-PGJ2 is generated as a consequence of dehydration of PGD2, a principal COX-2 product formed in various cells and tissues during the inflammatory processes [4]. PGD2 is spontaneously converted into prostaglandin J_2 (PGJ2), which undergoes intramolecular rearrangement of the 13,14-double bond followed by dehydration to form 15d-PGJ2 via Δ^{12}-PGJ2. Because of the electrophilic α,β-unsaturated carbonyl group present in its cyclopentenone ring, 15d-PGJ2 can act as a Michael addition acceptor and readily interacts with critical cellular nucleophiles, such as cysteine thiol groups of proteins. Many of the biological effects elicited by 15d-PGJ2 are mediated by modulating the activities of some key redox-transcription factors, such as nuclear factor-kappaB (NF-κB), signal transducers and activators of transcription 3 (STAT3), nuclear factor-erythroid 2p45 (NF-E2)-related factor (Nrf2), activator protein-1 (AP-1), hypoxia inducible factor, p53, thioredoxin, etc. (Fig. 2) [5]. However, the modulation of the aforementioned transcription factors and other signaling molecules by 15d-PGJ2 is not necessarily mediated via PPARγ activation, and in most cases, rather involves direct modification of their critical cysteine thiol groups that often serve as a redox-sensor. To better understand the role molecular recognition plays in the association of 15d-PGJ2 with putative target transcription factors, a docking strategy was applied along with calculation of *ab initio* electrostatic potential maps. Analysis of the mode of binding of 15d-PGJ2 with critical cysteine-containing sites localized in redox-sensitive transcription factors and their regulators identified some important sites that this electrophilic cyclopentenone prostaglandin recognizes and binds to with stability [6].

3. PGD2 synthase, a key enzyme in biosynthesis of 15d-PGJ2

15d-PGJ2 is produced as a consequence of a series of dehydration of PGD2. PGD2 synthase catalyzes the isomeric conversion of PGH2 to PGD2 in the presence of sulfhydryl compounds. When the amounts of major prostaglandins formed from arachidonic acid were determined in homogenates of various tissues of adult rats, PGD2 was the major one found in most tissues. The enzyme in the epididymis, brain, and spinal cord was found to be reduced glutathione (GSH)-independent PGD2 synthase [7]. The enzyme in the spleen, thymus, bone marrow, intestine, skin, and stomach was GSH-requiring PGD2 synthase [8]. The activity in the kidney and testis was catalyzed by GSH *S*-transferase. The activity in the liver, lung, adrenal gland, salivary gland, heart, pancreas, and muscle was due to both the GSH-requiring synthase and the transferase [9].

Two distinct types of PGD2 synthase were purified; one is the lipocalin-type enzyme, and the other is the hematopoietic enzyme [10]. cDNA and the genes for these enzyme were isolated, and the tissue distribution profiles and the cellular localization in several animal species were determined. Both enzymes are quite different from each other, in terms of their amino acid sequence, tertiary structure, evolutionary origin, chromosomal and cellular localization, tissue distribution, and also functional relevance. Lipocalin-type PGD2 synthase was found to be localized in the central nervous system (CNS) and male genital organs of various mammals as well as in the human heart. The human enzyme, initially identified at mass 19–24 kDa, was later characterized as beta-trace, which is a major protein in human cerebrospinal fluid. The levels of this enzyme were found to be reduced in the cerebrospinal fluid of patients with multiple sclerosis and schizophrenia [11]. When atherosclerotic plaques from patients who underwent carotid endarterectomy were analyzed, the prostaglandin E_2 (PGE2) pathway was significantly prevalent in symptomatic plaques, whereas the PGD2 pathway was overexpressed in asymptomatic ones, and the latter pathway was associated with NF-κB inactivation and matrix metalloproteinases (MMP)-9 suppression. These clinical findings suggest that the switch from lipocalin-type PGD synthase to inducible PGE synthase in plaque macrophages is associated with cerebral ischemic syndromes, possibly through MMP-induced plaque rupture [12].

Lipocalin-type PGD2 synthase is considered to have a dual-function; it acts as a PGD2-producing enzyme and also as a lipophilic ligand-binding protein, capable of physically interacting with retinoids, thyroids, and bile pigments with high affinities. Hematopoietic PGD2 synthase is widely distributed in the peripheral tissues and predominantly localized in the antigen-presenting cells, mast cells, and megakaryocytes. The hematopoietic enzyme is the first recognized vertebrate homolog of the sigma class of GSH *S*-transferase. PGD2 synthase gene-knockout mice and human enzyme-overexpressing transgenic mice were generated for functional studies [10,13].

Previous studies have demonstrated that PGD2 synthase, which is required for 15d-PGJ2 synthesis, is predominantly expressed in macrophages and specialized antigen-presenting cells [14]. Thus, when cellular localization of reduced GSH-requiring PGD2 synthase was investigated in adult rats, the positive immunocytochemical stain was found in a number of histiocytes and/or dendritic cells in spleen, thymus, and Peyer's patch of intestine. The immunostain was also observed in lamina propria of the villus in small intestine and colon, in submucosal layer of stomach, and in Kupffer cells in liver. These observations suggest that PGD2 synthase plays a critical role in dictating the progression of immune responses [14].

4. Protective effects of 15d-PGJ2 on experimentally induced inflammation

Living organisms have evolved sophisticated defense mechanisms that allow them to adapt to and survive a vast variety of stresses, including inflammatory insults. 15d-PGJ2 has been considered as a potential endogenous protectant counteracting deleterious actions of the pro-inflammatory response in various stressful conditions [15]. The following section deals with protective effects of 15d-PGJ2 against several experimentally induced inflammatory disorders in animals.

4.1. Protection against stress-induced cerebrospinal injury

Stress response affects many different organs and tissues, mainly CNS. Stress-related events (e.g., stroke, multiple sclerosis and traumatic injury) are characterized by increased plasma levels of tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators, but the physiological significance of such elevation

remains unknown. Stress also activates the transcription factor NF-κB that is widely expressed in the CNS. One of the activators of NF-κB is TNF-α. Two of the important target molecules of NF-κB are pro-inflammatory enzymes, inducible nitric oxide synthase (iNOS) and COX-2. iNOS catalyzes the formation of nitric oxide (NO) radical from L-arginine. It has been speculated that an excess of NO and related reactive nitrogen species as well as pro-oxidants formed in various brain areas are responsible for both impairment of neuronal functions and structural damage. Similarly, COX-2, another known source of oxidants as well as pro-inflammatory prostaglandins, may account for stress-induced brain damage. As in the case of iNOS, overexpression of COX-2 has been frequently observed in the brain during chronic stress and several neurological disorders, such as stroke, Alzheimer's dementia and seizures [15]. For instance, immobilization stress is accompanied by accumulation of nitrosative as well as oxidative mediators in brain after expression of iNOS and COX-2 as well as the release of TNF-α and other cytokines in the brain [16].

Despite abundant expression of lipocalin-type PGD2 synthase in the brain, the role of PGD2 and its terminal metabolite 15d-PGJ2 in brain protection remains unclear. Following acute restraint stress exposure of young-adult male Wistar rats for 6 h, there was COX-2 upregulation and subsequently pro-inflammatory PGE2 release (38 ± 5 pg/mg protein) in rat brain cortex. Concomitantly, the level of the 15d-PGJ2 was markedly elevated (427.83 ± 70 pg/mg protein) [17], constituting a possible endogenous local anti-inflammatory mechanism of defense against excessive neuroinflammation. Pharmacologic inhibition of COX-2 abrogated the stress-induced 15d-PGJ2 increase. Notably, injection of supraphysiological doses (*i.e.*, 80–120 μg/kg) of 15d-PGJ2 blunted the stress-induced increase in COX-2 expression and PGE2 release, suggesting a role for this cyclopentenone prostaglandin in the negative feedback loop of COX-2 expression. Similarly, iNOS activity and subsequent NO production during stress were attenuated by exogenous administration of 15d-PGJ2. In addition, injection of supraphysiological doses of 15d-PGJ2 (80–120 μg/kg) decreased stress-induced increase in iNOS activity as well as the stress-induced increase in NO metabolites. Moreover, 15d-PGJ2 attenuated the accumulation of malondialdehyde, a biochemical hallmark of lipid peroxidation, in the brain cortex of stressed animals, and prevented oxidation of the main antioxidant GSH. The anti-oxidative properties of 15d-PGJ2 in stressed animals were attributed to NF-κB blockade as well as inhibition of TNF-α release [16].

Focal cerebral ischemia was induced by middle cerebral/common carotid arteries occlusion in rats. Intraventricular injection of 15d-PGJ2 into the ischemic rat brains attenuated brain damage at 24 h after reperfusion as evidenced by the significantly reduced infarction volume [18]. In another study, adenoviral transfer of COX-1 amplified the production of 15d-PGJ2 in the cortex of ischemic brain in a rat focal infarction model. Cortical accumulation of 15d-PGJ2 was accompanied by the reduced infarct volume, a decrease in COX-2 expression and elevated heme oxygenase-1 (HO-1) expression. Intraventricular infusion of 15d-PGJ2 resulted in reduction of infarct volume. 15d-PGJ2 at low concentrations suppressed H_2O_2-induced rat or human neuronal apoptosis and necrosis and induced HO-1 expression. Thus, 15d-PGJ2 is likely to play a role in controlling acute cerebral injury caused by ischemia/reperfusion (I/R) [19].

Intrastriatal injection of 15d-PGJ2 in male Sprague–Dawley rats significantly increased catalase expression while the same treatment reduced NF-κB DNA binding, neutrophil infiltration, and also cell apoptosis in the affected striatum. In addition, 15d-PGJ2 ameliorated behavioral dysfunction caused by the intracerebral hemorrhage [20].

Fever, an important part of the host defense response, can be detrimental if uncontrolled. Intracerebroventricular infusion of 15d-PGJ2 (50 ng/μL at a rate of 25 μL/h) for 2 h significantly reduced the lipopolysaccharide (LPS)-induced fever in rats. In addition, 15d-PGJ2 and its synthesizing enzyme PGD2 synthase were present in rat cerebrospinal fluid, and their levels were elevated following systemic administration of LPS. The antipyretic effect of 15d-PGJ2 was associated with inhibition of LPS-induced COX-2 expression in the hypothalamus of rats [21].

Intraperitoneal administration of 15d-PGJ2 (200 μg/kg), given daily to Balb/c mice after experimentally induced spinal cord injury, significantly improved the sensory and locomotor function with increased neuronal survival. These changes were accompanied by a reduction in chemokine and pro-inflammatory cytokine expression [22].

The etiology as well as pathology of multiple sclerosis is complex and still poorly understood. It is characterized by inflammation, demyelination and axonal and neuronal degeneration. 15d-PGJ2 inhibited experimentally induced allergic encephalomyelitis (EAE), a Th1 cell-mediated autoimmune disease model of multiple sclerosis, by blocking IL-12 signaling, leading to Th1 differentiation [23]. Psychological stress has been suggested to be one of the trigger factors in the onset and/or relapse of symptoms. Twelve days of immobilization stress exposure exacerbated experimentally induced EAE in Dark Agouti rats. In addition, these animals presented higher levels of MMP-9 and pro-inflammatory PGE2 in spinal cord. In contrast, animals chronically exposed to stress (21 days) showed a significantly lower incidence of EAE clinical signs and reduced myelin loss, leukocyte infiltration and accumulation of inflammatory/oxidative mediators in spinal cord. Interestingly, chronically stressed animals showed a parallel increase in levels of the anti-inflammatory prostaglandin 15d-PGJ2. These results demonstrate that stress exposure, depending on duration, elicits opposite effects on EAE as well as differentially alters the PGE2/15d-PGJ2 ratio in the spinal cord of Dark Agouti rats [24].

4.2. Protection against endothelial/vascular damage (atheroprotective effects)

15d-PGJ2 has been reported to exert atheroprotective effects by inhibiting vascular inflammation [25]. Vascular endothelial cells, intimal smooth muscle cells, and cardiomyocytes express lipocalin-type PGD2 synthase, an enzyme that catalyzes the isomerization of PGH2 to PGD2. When endothelial cells were challenged with laminar fluid shear stress, the expression of PGD2 synthase was increased, and PGD2 and 15d-PGJ2 were detected in the culture medium. Based on these findings, it is speculated that 15d-PGJ2 is a physiological substance produced in the vascular wall to protect vascular endothelial cells from noxious stimuli and to repress inflammatory reactions [25].

4.3. Protection against pulmonary damage

Multiple factors contribute to the pathogenesis and prognosis of chronic obstructive pulmonary disease (COPD). Wistar rats treated with intratracheal LPS up to 6 weeks developed pathogenic conditions mimicking COPD, such as chronic lung hyperinflation and hypertrophy, increased alveolar enlargement, reduced vascular endothelial growth factor and elevated tissue inhibitor of MMP-1 levels in bronchoalveolar lavage fluid, and early changes of leukocyte influx and interferon-γ (IFN-γ) levels in bronchoalveolar lavage fluid. Oral administration of 15d-PGJ2 at the daily doses of 1 and 10 mg/mL per kg body weight ameliorated these changes in a dose-dependent fashion [26].

After carrageenin injection, acute pulmonary inflammation characterized by alveolar oedema and the infiltration of neutrophils into the airspaces was observed in Balb/c mice. Pulmonary inflammation was also assessed using lung digests and bronchoalveolar lavage. While none of the cells recovered from the

bronchoalveolar lavage fluids before carrageenin injection was positive for the anti-15d-PGJ2 antibody, there was marked accumulation of 15d-PGJ2 in alveolar macrophages, but not in neutrophils, on days 1 and 3 after carrageenin injection. Treatment of mice with a selective COX-2 inhibitor NS-398 significantly attenuated the pulmonary accumulation of 15d-PGJ2 and exacerbated acute lung injury. The intratracheal administration of 15d-PGJ2 (100 μg/kg) reversed the pathologic changes in the lungs of NS-398-treated mice [27].

4.4. Protection against gastrointestinal injury

Psychological stress has been implicated in the clinical course of several gastrointestinal disorders. Male Wistar rats challenged with acute immobilization stress for 6 h showed a marked increase in myeloperoxidase (MPO) activity and expression of iNOS and COX-2 as well as production of PGE2 in colon. The expression of constitutive isoforms, nNOS and COX-1, remained unchanged. In parallel with the increases in activity/expression of pro-inflammatory molecules, there was a significant elevation of colonic 15d-PGJ2 levels. Intraperitoneal administration of 15-PGJ2 (120 μg/kg) prior to exposure to stress prevented the weight loss and an increase in MPO activity. 15d-PGJ2 pretreatment also attenuated the expression of iNOS expression, but not of COX-2. Interestingly, the colonic level of PGE2, a major product of COX-2, was reduced in the colon of 15d-PGJ2 pretreated mice. These findings suggest that 15d-PGJ2 is likely to protect against colonic inflammation and dysfunction caused by stress [28].

Enterocolitis is characterized by disruption of the mucosal barrier, transmural intestinal injury and significant inflammatory response typically involving terminal ileum and colon. It is the most common gastrointestinal surgical emergency, resulting in a lethal condition for many premature infants. Swiss-Webster mice subjected to I/R injury exhibited significant villous destruction in both jejunum and ileum, consistent with pathological features of necrotizing enterocolitis. There was a substantial increase in the NF-κB DNA binding in small intestine during I/R-induced intestinal injury. Pretreatment with an intraperitoneal dose (2 mg/kg) of 15d-PGJ2 significantly attenuated intestinal NF-κB activation and gut injury, preserving the mucosal structural integrity similar to the control intestinal sections, in a murine model of necrotizing enterocolitis [29].

Acute inflammation, including neutrophil activation, plays a critical role in the pathogenesis of I/R. Gastric mucosal damage was induced in male Wistar rats by clamping the celiac artery for 30 min followed by reperfusion. Intraperitoneal administration of 15d-PGJ2 (0.01–1.0 mg/kg) 1 h prior to I/R reduced the severity of acute gastric mucosal injury in rats. The gastroprotective effects of 15d-PGJ2 were attributed, in part, to a reduction in the infiltration of neutrophils into the gastric mucosa, possibly through the inhibition of inflammatory cytokine production [30].

4.5. Cardioprotection

In a rat model of regional myocardial I/R, administration (i.v.) of 15d-PGJ2 and prostaglandin A_1 (PGA1) caused a pronounced reduction of the myocardial infarct size. The cardioprotective effect of 15d-PGJ2 was associated with decreased expression of the adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and P-selectin, chemokine macrophage chemotactic protein 1 (MCP-1), and iNOS [31]. 15d-PGJ2 also reduced the nitration of proteins in the myocardium of the rats subjected to I/R, likely due to the generation of peroxynitrite.

Myocardial I/R in male Wistar rats resulted in elevated tissue activity of MPO, indicative of infiltration of neutrophils, and elevated plasma levels of creatine kinase and TNF-α. All these events were attenuated by treatment with 15d-PGJ2. The cardioprotective effects of 15d-PGJ2 were associated with suppression of NF-κB activation. Treatment with 15d-PGJ2 also enhanced DNA binding of heat shock factor 1 and upregulated the expression of the cardioprotective heat shock protein 70 [32].

Administration of 15d-PGJ2 substantially ameliorated experimental autoimmune myocarditis and suppressed myocardial expression of inflammatory cytokines in rats. In addition, 15d-PGJ2 treatment enhanced IκB levels in both cytoplasmic and nuclear fractions from inflammatory myocardium. Concurrently, NF-κB activation was markedly elevated in myocarditis, and this was repressed in the 15d-PGJ2-treated groups [33].

Remote ischemic preconditioning (remote IPC) elicits a protective cardiac phenotype against myocardial ischemic injury. Male New Zealand white rabbits were subjected to a 30-min coronary artery occlusion followed by 3 h of reperfusion. Three cycles of remote IPC consisting of 10-min renal I/R were performed. The remote IPC significantly reduced the myocardial infarct size, which was accompanied by increased iNOS expression as well as 15d-PGJ2 levels (179.7 ± 7.9 pg/mL vs. 127.9 ± 7.6 pg/mL) [34].

4.6. Protection against pancreatitis

Acute pancreatitis can be induced in mice and rats by hyperstimulation with the cholecystokinin analogue, cerulein. Cerulein-induced pancreatitis is similar to human edematous pancreatitis, which is characterized by dysregulation of digestive enzyme production, cytoplasmic vacuolization, and increased cytokine production. Pretreatment of male Sprague–Dawley rats with an intraperitoneal dose (10 mg/kg body weight) of 15d-PGJ2 attenuated severity of cerulein-induced pancreatitis as evidenced by reduced oedema and vacuolization and α-smooth muscle actin (α-SMA) gene expression [35]. Similarly, pretreatment of mice with 15-PGJ2 significantly reduced serum amylase activity and histological features (e.g., leukocyte infiltration, necrosis, and vacuolization). There was also upregulation of pro-inflammatory cytokines, interleukine (IL)-6 and TNF-α [36]. Swiss Webster mice were injected with either saline or cerulein eight times at 1-h intervals and received either 15d-PGJ2 (2 mg/kg) or vehicle 1 h before and 4 h after induction of acute pancreatitis. Administration of 15d-PGJ2 attenuated cerulein-induced acute pancreatitis in mice, which was associated with decreased expression of COX-2 and ICAM-1 and reduced levels of serum and pancreatic IL-6 [37].

4.7. Protection against rheumatoid arthritis

Rheumatoid arthritis is a chronic polyarticular joint disease associated with massive synovial proliferation, inflammation, and angiogenesis. 15d-PGJ2 inhibits the growth of rheumatoid synoviocytes *in vitro*, and suppresses the chronic inflammation of adjuvant-induced arthritis in rats. PGE2 is considered to play important roles in joint erosion and synovial inflammation. 15d-PGJ2 suppressed interleukin IL-1β-induced PGE2 synthesis in rheumatoid synovial fibroblasts by inhibiting expression of COX-2 and cytosolic phospholipase A2. In this context, 15d-PGJ2 is a key regulator of negative feedback of the arachidonic acid cascade in the COX pathway [38].

4.8. Protection against other inflammatory injuries

Cyclophosphamide injection causes severe cystitis (bladder inflammation) in male Sprague–Dawley rats. Intraperitoneal administration of 15d-PGJ2 ameliorated the development of cystitis and reduced the increase in vascular permeability, expression and enzymatic activity of iNOS, urinary excretion of NO metabolites, MPO activity, IL-1β production in the bladder of

cyclophosphamide-treated rats [39]. It'll be worthwhile clarifying whether endogenous 15d-PGJ2 plays a role in the natural remodeling process after cyclophosphamide treatment.

Multiple-organ failure is characterized by the progressive deterioration in the function of several organs or systems in patients with septic shock, multiple trauma, severe burns, or pancreatitis. 15d-PGJ2 inhibited the inflammatory response and significantly reduced peritoneal mononuclear cell infiltration and histological injury in a mouse model of zymosan-induced nonseptic shock. A protection was demonstrated in kidney, liver, and pancreas. 15d-PGJ2 also reduced the appearance of nitrotyrosine in the inflamed intestinal tissues. Histological examination revealed a significant reduction in zymosan-induced intestinal damage in 15d-PGJ2-treated mice [40].

Major trauma/injury causes a dramatic host response that disrupts cellular immune homeostasis and initiates an inflammatory cascade that predisposes the injured host to subsequent infections. 15d-PGJ2 treatment reduced the levels of inflammatory mediators produced by splenic macrophages 7 days after injury. Furthermore, treatment of injured mice with 15d-PGJ2 conferred a survival advantage after infectious challenge induced by cecal ligation and puncture [41].

Intraplantar administration of 15d-PGJ2 (30–300 ng/paw) inhibited the mechanical hypernociception caused by both carrageenan (100 μg/paw) and the directly acting hypernociceptive mediator, PGE2 [42].

Carrageenan administration causes pleurisy in mice. It was observed that 15d-PGJ2 predominantly accumulated in macrophages from pleural lavage of carrageenan-treated mice, suggesting that 15d-PGJ2 may act through modifying macrophage function. Administration of the selective COX-2 inhibitor NS-398 to mice with carrageenan-induced pleurisy caused persistence of neutrophile recruitment. Simultaneous injection of 15d-PGJ2 (100 μg/kg) with carrageenan into the pleural space reversed the increase of neutrophil infiltration in the NS-398-treated mice [43].

In the rat carrageenin-induced acute inflammation model of pleurisy, COX-2 protein expression peaked initially at 2 h, concurrently with maximal PGE2 synthesis. However, at 48 h, there was a second increase in COX-2 expression, but this was associated with minimal PGE2 synthesis, while the levels of PGD2 and 15d-PGJ2 were elevated. The selective COX-2 inhibitor NS-398 and the dual COX-1/COX-2 inhibitor indomethacin attenuated inflammation at 2 h but significantly exacerbated inflammation at 48 h. This exacerbation was associated with reduced PGD2 and 15d-PGJ2 concentrations, and was reversed by replenishment of these prostaglandins [44]. Likewise, the selective inhibition of COX-2 ameliorated inflammatory cell apoptosis, resulting in an increase in total inflammatory cell numbers, and these effects were reversed, in part, by 15d-PGJ2 administration [45].

5. Mechanisms underlying anti-inflammatory effects

15d-PGJ2 contains two α,β-unsaturated ketone moieties in tandem within its structure, but the one comprising the cyclopentenone ring structure appears to be more electrophilic. Thus, the majority of activities of 15d-PGJ2 are likely to be due to the reactive α,β-unsaturated carbonyl group located in the cyclopentenone ring. 15d-PGJ2 can covalently modify critical proteins in multiple pathways, altering their conformations and subsequently, influencing the expression of effector genes.

15d-PGJ2 down-regulates expression or activity of pro-inflammatory signaling molecules induced by various stimuli (e.g., TNF-α, IL-1β, LPS, phorbol ester, etc.) in several cell lines (*vide infra*). Table 1 summarizes the expression/production of various pro- and anti-inflammatory signaling molecules modulated by 15d-PGJ2. 15d-PGJ2 has been reported to inhibit the expression of a number of proteins involved in the pathogenesis of arthritis. However, its effects on COX-2 remain controversial. In human synovial fibroblasts, IL-1β-induced expression of COX-2 and its mRNA transcript as well as COX-2 promoter activation was inhibited by 15d-PGJ2 [46]. Furthermore, 15d-PGJ2 blocked IL-1β-induced recruitment of p300 to the COX-2 promoter, which may account for decreased histone H3 acetylation and COX-2 expression. In accordance with this, overexpression of p300, but not of a mutant p300 lacking histone acetyltransferase (HAT) activity, relieved the inhibitory effect of 15d-PGJ2 on COX-2 promoter activation. These data suggest that 15d-PGJ2 can inhibit IL-1β-induced COX-2 expression by a histone deacetylase (HDAC)-independent mechanism, probably by interfering with the HAT p300 [46]. In contrast to these observations, 15d-PGJ2 treatment to serum-deprived human mesangial cells upregulated COX-2 protein expression, but not COX-1 [47]. Interestingly, enhanced expression of COX-2 by 15d-PGJ2 did not result in increased PGE2 production, but rather inhibited IL-1β-induced PGE2 production. These results indicate that 15d-PGJ2 inhibits PGE2 production, independently of its effect on COX-2 expression [47]. The thiol reducing antioxidant *N*-acetylcysteine (NAC) almost completely abolished 15d-PGJ2-dependent COX-2 upregulation. This effect of NAC seemed to be specific for 15d-PGJ2 since upregulation of COX-2 by PGE2, IL-1β or prostaglandin A_2 (PGA2) was unaffected by preincubation with NAC. Pretreatment of human mesangial cells with buthionine sulfoximine (BSO), an inhibitor of GSH biosynthesis, augmented 15d-PGJ2-induced increase of COX-2 expression in a synergistic manner. 15d-PGJ2-induced an intracellular ROS accumulation which was inhibited by preincubation with NAC. However, the increase of COX-2 expression by 15d-PGJ2 does not appear to be mediated through enhanced ROS production. In contrast to 15d-PGJ2, PGA2, which also contains an α,β-unsaturated keto group in the cyclopentenone ring, elicited an increase in PGE2 production, which was enhanced synergistically with IL-1β. These effects of PGA2 were not affected by NAC [47]. The differences in the electrophilic potential of PGA2 and 15d-PGJ2 may account for their differential effects on PGE2 production. It is noticeable that the carbonyl group in the cyclopentenone ring of 15d-PGJ2 is conjugated to an additional double bond located in the side chain (Fig. 1), which may potentiate the electrophilic nature of this cyclopentenone prostaglandin, compared with PGA2. In line with this speculation, our previous studies demonstrated that 15d-PGJ2 stabilized p53 tumor suppressor protein to a greater extent than did PGA2 when treated to human breast cancer MCF-7 cells [48].

15d-PGJ2 and another cyclopentenone prostaglandin, PGA1 have been reported to exhibit anti-inflammatory activity in activated monocytes/macrophages. However, the effects of these two cyclopentenone prostaglandins on the expression of cytokine genes may differ. Thus, 15d-PGJ2 inhibited the expression of LPS-induced IL-10 expression in mouse peritoneal macrophages, whereas PGA1 synergistically increased it [49].

5.1. Suppression of IκB kinase-NF-κB signaling

The ubiquitous eukaryotic transcription factor NF-κB and its activating kinases play essential roles in cellular inflammatory signaling and hence are key targets for the anti-inflammatory activity of 15d-PGJ2 [3]. NF-κB is normally sequestered in the cytoplasm as an inactive complex with a family of repressors, such as inhibitory protein κB (IκBα). One of the essential components of NF-κB signaling is the IκB kinase (IKK) complex that phosphorylates IκBα, triggering its conjugation with ubiquitin and subsequent degradation. As a result, NF-κB is liberated from the inhibitory protein and translocates to the nucleus. This, in turn, induces expression of target genes, including the one for COX-2,

Table 1
Regulation of inflammation signaling by 15d-PGJ2.

Signal	Endpoint	Cell type	Stimulus	Effects	Reference
NF-κB signaling	NF-κB activation ↓	Human chondrocytes	IL-1β	COX-2 expression ↓	[58]
		Rat cardiac myocytes	H_2O_2	TNF-α production ↓	[63]
		Primary amnion		COX-2 expression ↓	[64]
		WISH cells	TNF-α	PGE2 production ↓	
		HUVECs		NF-κB activation ↓	[75]
		Breast cancer cells	TNF-α	Antiapoptotic proteins ↓ (Induction of apoptosis, caspase activation)	[76]
	NF-κB DNA binding activity ↓	A549 cells	RSV infection	TNF-α, GM-CSF, IL-1, IL-6, chemokines CXCL8 (IL-8) and CCL5 (RANTES) ↓	[67]
		HT-29	TNF-α		[29]
	NF-κB luciferase reporter ↓	Human astrocytes	IL-1	Cytokines (TNF-α, IL-6), Chemokines (RANTES/CCL5 and I P10/CXCL10) and iNOS ↓	[55]
		Human chondrocytes	IL-1β TNF-α IL-17	no and MMP-13 ↓	[57]
	IκBα degradation ↓	Pancreatic stellate cells	PDGF	Cell cycle progression by G1 phase and proliferation ↓	[62]
		Osteoblast-like mC3T3E-1 cells	LPS	IL-6 ↓	[70]
		HT-29	LPS	COX-2, IL-8, TLR4 ↓	[77]
		Raw 264.7	LPS/IFN-γ	NO synthesis, iNOS and COX-2 ↓	[53]
	IKK activation 4 ↓	Human synovial fibroblast	TNF-α	MMP-13 ↓	[68]
		Raw 264.7	LPS/IFN-γ	NO synthesis, iNOS and COX-2 ↓	[53]
	IKKβ phosphorylation ↓	Rat primary astrocytes	LPS/IFN-γ	iNOS, TNF-α, IL-1β, IL-6 ↓	[54]
	JNK and p38 phosphorylation ↓	Human astrocyte	IL-1	Cytokines (TNF-α, IL-6) ↓ Chemokines (RANTES/CCL5 and IP10/CXCL10) and iNOS ↓	[55]
	ERk1 and p38 phosphorylation ↓	Dendritic cells	TLR ligands	Differentiation of dendritic cells ↓	[66]
	ERK1/2 ↓	Human macrophages and endothelial cells	LPS/TNF-α	Tissue factor (TF) ↓	[56]
	Akt phosphorylation ↓	Rat primary astrocytes	LPS/IFN-γ	iNOS, TNF-α, IL-1β, IL-6 ↓ (Recruitment of p300 by p65 ↓)	[54]
	NF-κB activation ↓	Nephritic rats (p.o.)	ATS	Glomerulonephritis ↓	[51]
	NF-κB DNA binding activity ↓ (IκB degradation ↓)	Swiss Webster mice (i.p.)	Ceruleine	Pancreatitis ↓	[37]
	IκBα degradation ↓	Wistar Rats (i.p.)	Immobilization stress I/R	iNOS and TNF-α ↓	[15]
		Rat cardiac tissue (i.p.)		Cardioprotective effects Acute myocardial infarction	[31]
STAT3-JAK signaling	STAT3 activation ↓	Primary human monocytes/ macrophages/THP-1	IL-10 IFN-γ	Inflammation ↓	[127]
		CD133 positive-BTSCs	EGF/bFGF	Glio sphere formation ↓ Glioma and gliosphere cell proliferation and expansion ↓ Cell cycle arrest and apoptosis ↑	[86]
	JAK phosphorylation ↓	SCC	TGFα/IL-6	Apoptosis ↑	[87]
		ES cells	LIF	Proliferation and self-renewal ↓	[88]
	SOCS1 and 3 and Src homology 2 domain-containing protein phosphatase 2 ↑	Astrocytes and microglia		Inflammation ↓	[85]
	SOCS1 ↑	Balb/c mice (IP)	Injured spinal cord	Sensory and locomotor function ↑	[22]
	SOCS3 ↑	AR42J cells	Cerulein	IL-6 and TGFβ ↓	[35]
		Rats (IP)	Cerulein	Pancreatitis ↓	[35]
Nrf2-Keap1 signaling	Nrf2 activation ↑	Mouse peritoneal macrophages		HO-1 and PrxI gene expression ↑	[43]
		Glial cells		HO-1 expression ↑	[95]
		Hepatocytes		HO-1 expression ↑	[96]
		Macrophages		HO-1 expression ↑	[43,97]
		Myocytes		HO-1 expression ↑	[31]
		Lymphocytes		HO-1 expression ↑	[98,99]
		Mesangial cells		HO-1 expression ↑	[100]
		PC12 cells		HO-1 expression ↑	[102]
		PC12 cells		Cellular GSH by GCL expression ↑	[105]
		HAECs		Anti-atherosclerotic gene expression ↑	[106]
	Nrf2 nuclear translocation ↑	VSMCs		HO-1 expression ↑	[101]
	Keap1 binding ↑	Rat hepatocytes		15d-PGJ2 and Keap1 binding ↑	[43]
	Nrf2-mediated transcriptional pathway ↑	Nrf2-knockout mice (i.p.)	ALI model	Acute lung injury (ALI) ↓	[27]

which catalyzes the synthesis of pro-inflammatory prostaglandins, in particular PGE2. At late stages of inflammatory episodes, however, COX-2 directs the synthesis of anti-inflammatory cyclopentenone prostaglandins including 15d-PGJ2 and PGD2, suggesting involvement of these molecules in the resolution of inflammation [50]. The role for 15d-PGJ2 in the resolution of inflammation will be discussed more in detail in the later part of this article (see Section 6).

It has been previously demonstrated that cyclopentenone prostaglandins inhibit NF-κB activation induced by inflammatory cytokines, mitogens, and viral infection. The direct modification and consequent inactivation of the IKKβ subunit of the IKK complex has been suggested as a principal mechanism responsible for anti-inflammatory activity of 15d-PGJ2 and structurally related electrophilic cyclopentenone prostaglandins [50]. However, the anti-inflammatory effects of 15d-PGJ2 are mediated not only through IKK inhibition but also blockade of nuclear translocation and DNA binding of NF-κB, thereby dampening NF-κB-mediated transcriptional activation [1–3].

5.1.1. Animal studies

15d-PGJ2 has been reported to protect against pancreatitis produced in cerulein-treated mice. 15d-PGJ2 administration markedly suppressed NF-κB DNA binding activity, with concomitant inhibition of IκB protein degradation [37]. In an experimental model of glomerulonephritis, nephritic rats were treated with 15d-PGJ2 (1.5 mg/day). Twenty-four hours after induction of glomerulonephritis, the glomerular mRNA expression of MCP-1 and the cognate chemokine receptor CCR-2 were examined. Induction of glomerulonephritis was accompanied by enhanced nuclear protein binding of NF-κB and AP-1. 15d-PGJ2 administration attenuated NF-κB activation, but did not affect AP-1 activity or MCP-1 expression [51]. 15d-PGJ2 has been reported to prevent the inflammatory and oxidative/nitrosative damages in the CNS of rats subjected to immobilization stress. The mechanisms by which 15d-PGJ2 prevents these effects include inhibition of stress-induced increase in iNOS activity, NF-κB blockade (by preventing stress-induced IκBα degradation) and inhibition of TNF-α release in stressed animals. Other research has indicated the capacity of 15d-PGJ2 to reduce the expression of TNF-α, MMP-9/gelatinase B, COX-2 and iNOS in LPS-stimulated macrophages, glial cells and neurons. These proteins contribute to the inflammatory damage observed in certain neurological diseases [15,16].

15d-PGJ2 was found to exert cardioprotective effects in a rat model of acute myocardial infarction. In this study, the levels of IκBα in the cytosolic fraction of biopsies obtained from hearts subjected to I/R were significantly reduced. 15d-PGJ2 administration prevented I/R-induced IκBα degradation in the cardiac tissue [31].

5.1.2. Cell culture studies

Murine J774.2 macrophages were stimulated with bacterial LPS in the absence and presence of 15d-PGJ2. When added to the cells, 15d-PGJ2 reduced the LPS-induced NO and TNF-α production and the iNOS expression, and partially maintained mitochondrial respiration. The anti-inflammatory effects of 15d-PGJ2 were associated with down-regulation of NF-κB [52].

Treatment of the murine macrophage RAW 264.7 cells with 15d-PGJ2 inhibited the LPS- and IFN-γ-induced synthesis of NO. Incubation of activated macrophages with 15d-PGJ2 blocked the degradation of IκBα and IκBβ and increased their levels in the nuclei. NF-κB activity, as well as the transcription of NF-κB-dependent genes, such as those encoding iNOS and COX-2 was impaired under these conditions. Analysis of the steps leading to IκB phosphorylation showed an inhibition of IKK by 15d-PGJ2 in cells treated with LPS and IFN-γ, resulting in an impaired phosphorylation of IκBα. Incubation of partially purified activated IκB kinase with 15d-PGJ2 reduced the phosphorylation in serine 32 of IκBα, suggesting that this prostaglandin exerts direct inhibitory effects on the activity of the IκB kinase complex [53].

In primary astrocytes prepared from rat cerebral tissues stimulated with LPS/IFN-γ, 15d-PGJ2 inhibited the production or mRNA expression of iNOS and some pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6. 15d-PGJ2 inhibited the recruitment of p300 by p65 subunit of NF-κB and subsequently NF-κB luciferase reporter activity. The treatment with 15d-PGJ2 inhibited phosphorylation and catalytic activity of IKKβ as well as Akt phosphorylation [54].

The role of 15d-PGJ2 in human astrocyte activation was investigated. 15d-PGJ2 treatment inhibited a broad range of astrocyte inflammatory gene expression induced by IL-1. These include cytokines (TNF-α and IL-6), chemokines (RANTES/CCL5 and IP-10/CXCL10) and iNOS. 15d-PGJ2 inhibited transactivation of NF-κB-dependent promoters as well as phosphorylation of c-Jun N-terminals kinase (JNK) and p38 mitogen activated protein kinase (MAPK) induced by IL-1 [55].

Basic and clinical evidence has provided insight into the molecular events that link inflammation and coagulation. Increased expression of tissue factor (TF) by circulating and vascular cells is considered to be responsible for the thrombotic complications associated with acute and chronic inflammation. 15d-PGJ2 down-regulated LPS- and TNF-α-induced TF activity and expression through inhibition of TF gene transcription, which was mediated by targeting NF-κB and extracellular-regulated protein kinase (ERK)1/2. In this study, 15d-PGJ2 negatively affected TF expression in macrophages and endothelial cells through a PPARγ-independent mechanism [56].

Treatment of human chondrocytes with 15d-PGJ2 decreased production of NO and MMP-13 by IL-1β, TNF-α and IL-17. IL-1β induced mRNA expression of both iNOS and MMP-13, which are effector molecules upregulated by NF-κB, and this was inhibited in the presence of 15d-PGJ2. TNF-α- and IL-17-induced production of NO and MMP-13 was also attenuated by 15d-PGJ2. 15d-PGJ2 inhibited NF-κB-luciferase reporter gene activity through suppression of MAPK kinase (MEKK1) [57]. 15d-PGJ2 was also highly potent to counteract IL-1β-induced COX-2 expression and NF-κB activation [58]. Microsomal prostaglandin E synthase (mPGES)-1 is an inducible enzyme of the arachidonic acid cascade with a key function in PGE2 synthesis. This enzyme is functionally coupled with COX-2 and converts the COX product PGH2 to PGE2. The expression of mPGES-1 was found to be markedly elevated in human osteoarthritic cartilage compared with normal cartilage [59]. Treatment of human chondrocytes with IL-1β induced expression of mPGES-1 protein. TNF-α and IL-17 also upregulated expression of mPGES-1 protein and displayed a synergistic effect with IL-1β. 15d-PGJ2 inhibited IL-1β-induced mPGES-1 protein expression, an effect that was reversed by exogenous PGE2 [59].

15d-PGJ2 decreased degradation of IκBα degradation without influencing its phosphorylation by specifically inhibiting IKKβ, but not IKKα enzymatic activity in IL-1β-treated rat chondrocytes [60]. 15d-PGJ2 (0.1–10 μM) dose-dependently decreased PGE2 production in rat chondrocytes stimulated with IL-1β [61]. 15d-PGJ2 inhibited expression of mPGES-1 as well as COX-2 at both the mRNA and protein levels in IL-1β stimulated rat chondrocytes, and these effects were attributed to its suppression of NF-κB [61].

Activated pancreatic stellate cells are implicated in the pathogenesis of pancreatic fibrosis and inflammation. 15d-PGJ2 inhibited platelet-derived growth factor (PDGF)-induced proliferation in rat pancreatic stellate cells. The anti-proliferative effect of 15d-PGJ2 was associated with inhibition of cell cycle progression beyond the G1 phase. PDGF-induced expression of α-SMA protein, α1(I) procollagen and prolyl 4-hydroxylase(α), and inducible

MCP-1 was also down-regulated by 15d-PGJ2 treatment. 15d-PGJ2 inhibited the degradation of IκBα and consequent NF-κB activation [62].

Pretreatment of rat cardiac myocytes with 15d-PGJ2 suppressed the H_2O_2-induced TNF-α production (mRNA and protein) and NF-κB activation [63]. In another study, 15d-PGJ2 inhibited COX-2 expression and PGE2 production in primary amnion and WISH cells stimulated with TNF-α, which appeared to be associated with blockade of NF-κB activity [64]. Mouse neonatal cardiomyocytes stimulated with LPS exhibited increased expression of iNOS, COX-2 and MMP-9, which was inhibited with 15d-PGJ2 by targeting NF-κB and p38 MAPK [65].

The antigen-presenting dendritic cells play an essential role in initiating and maintaining primary immune responses. However, mechanisms involved in the termination of these responses are elusive. The effects of 15d-PGJ2 on the immunogenicity of human peripheral blood-adhering monocyte-derived dendritic cells were examined upon stimulation with toll-like receptor (TLR) ligands. The NF-κB family of transcription factors are known to be important for the differentiation and function of dendritic cells. The inhibition of the MAPK and NF-κB pathways is critically involved in the regulation of TLR-mediated activation of dendritic cells. 15d-PGJ2 inhibited the phosphorylation of ERK1 and p38 MAPK and nuclear accumulation of NF-κB in dendritic cells [66]. The epithelial cells of the airways are the target cells for respiratory syncytial virus infection and the site of the majority of the inflammation associated with the disease. 15d-PGJ2 inhibited the release of pro-inflammatory cytokines TNF-α, GM-CSF, IL-1, IL-6 and the chemokines CXCL8 (IL-8) and CCL5 (RANTES) from RSV-infected human lung epithelial (A549) cells. Concomitantly, 15d-PGJ2 diminished the expression of mRNA transcripts of IL-6, CXCL8 and CCL5 and the RSV-induced DNA binding activity of NF-κB (p65/p50) and AP-1 (c-Fos) [67].

15d-PGJ2 markedly inhibited TNF-α-induced MMP-13 production in human synovial fibroblasts, and these effects appear to be associated with its direct inactivation of IKK via a PPARγ-independent manner [68]. When treated to rat synovial fibroblasts, 15d-PGJ2 dose-dependently decreased LPS-induced COX-2 and iNOS mRNA expression [69]. LPS-induced IL-1β and TNF-α expression was also attenuated by 15d-PGJ2 treatment. In this study, 15d-PGJ2 inhibited DNA binding activity of both NF-κB and AP-1 [69]. Periodontitis is a chronic inflammatory disease characterized by gingival inflammation and periodontal tissue destruction, leading to alveolar bone resorption and eventual tooth loss. 15d-PGJ2 inhibited LPS-stimulated IL-6 production by blocking the IκBα degradation and subsequent nuclear translocation of the p65 subunit of NF-κB in osteoblast-like MC3T3E-1 cells [70].

Lectin-like oxidized low-density lipoprotein receptor1 has been recognized to be the major endothelial receptor for oxidized low-density lipoprotein (ox-LDL). Ox-LDL has been reported to induce the expression of inflammatory adhesive molecules from vascular endothelium. Preincubating human vascular endothelial cells (HUVECs) with 15d-PGJ2 attenuated the expression of ICAM-1 and E-selectin in response to ox-LDL, although ox-LDL [71].

IL-8 is one of cytokines detected at sites of inflammation and in macrophage-foam cells of atherosclerotic lesions. The expression of IL-8 gene can be induced in cholesterol loaded human monocyte leukemia THP-1 cells by ox-LDL. The expression of human IL-8 gene in THP-1 cells was upregulated by 15d-PGJ2. 15d-PGJ2-induced expression of IL-8 gene through a MAPK signaling pathway. Pyrrolidine dithiocarbamate, an antioxidant with NF-κB inhibitory activity, augmented 15d-PGJ2-mediated upregulation of IL-8 gene expression [72]. Similarly, treatment of human microvascular endothelial cell line (HMEC-1) with LPS increased the pro-inflammatory IL-8 secretion. 15d-PGJ2 potently increased both the steady-state and LPS-induced expression of both IL-8 as well as mRNA [73].

Inflammation often induces enhanced expression of specific cell adhesion molecules in activated vascular endothelial cells, which increases the adhesion and infiltration of leukocytes. TNF-α, as a prototypic pro-inflammatory cytokine, causes endothelial dysfunction through activation of NF-κB, a key transcription factor that regulates expression of cell adhesion molecules. 15d-PGJ2 has anti-inflammatory properties in endothelial cells. Thus, 15d-PGJ2 inhibited TNF-α-induced monocyte adhesion to endothelial cells, which was mediated by down-regulation of endothelial cell adhesion molecules. These effects were mediated by inhibiting the TNF-α-induced activation of IKK and NF-κB by 15d-PGJ2 [74]. Likewise, pretreatment of HUVECs with 15d-PGJ2 abrogated the TNF-α-induced NF-κB activation [75].

NF-κB is constitutively activated in many cancerous and transformed cells and is considered a potential target for chemo- and radiation therapy. 15d-PGJ2 is a potent inhibitor of constitutive IKK and NF-κB activities in chemotherapy-resistant estrogen receptor-negative breast cancer cells. 15d-PGJ2-induced inhibition of NF-κB function caused down-regulation of antiapoptotic proteins (e.g., cIAPs 1/2, Bcl-X_L, and cellular FLICE-inhibitory protein), leading to caspase activation and induction of apoptosis in breast cancer cells resistant to treatment with paclitaxel and doxorubicin [76].

Pretreatment of human HT-29 intestinal epithelial cells with 15d-PGJ2 resulted in significant attenuation in TNF-α-induced NF-κB DNA binding activity [29]. HT-29 human intestinal epithelial cells were stimulated with LPS in the presence or absence of 15d-PGJ2 for 24 h. 15d-PGJ2 cotreatment decreased LPS-induced mRNA expression of COX-2, IL-8 and TLR4 and secretion of IL-8. 15d-PGJ2 also retarded LPS-induced IκBα degradation [77].

5.2. Suppression of STAT3-Janus kinase signaling

Besides NF-κB, STAT3 has been recognized as an important mediator of inflammation signaling. Persistently activated STAT3 stimulates proliferation, survival and invasion of tumor cells, while suppressing anti-tumor immunity. Recently, special attention has been focused on the interplay or cross-talk between NF-κB and STAT3 in controlling the dialog between the malignant cells and its microenvironment, especially with inflammation/immune cells that infiltrate tumors [78]. Thus, IKK-NF-κB and STAT3 pathways are like central signaling hubs in inflammation-mediated tumor promotion and progression [78].

In rat microglial cells stimulated by LPS, IFN-γ or by their combination, 15d-PGJ2 reduced the production of NO and the expression of iNOS. In addition, 15d-PGJ2 down-regulated other microglial functions, such as TNF-α synthesis and expression of major histocompatibility complex class I. The effects of 15d-PGJ2 occurred, at least in part, through the repression of two important transcription factors, STAT1 and NF-κB, known to mediate IFN-γ and LPS cell signaling [79].

5.2.1. Animal studies

BALB/c mice were experimentally subjected to spinal cord injury. Intraperitoneal administration of 15d-PGJ2 significantly improved the sensory and locomotor function of the damaged mice. These changes were accompanied by a reduction in chemokine and pro-inflammatory cytokine expression. Suppressor of cytokine signaling (SOCS) is a negative feedback regulator of Janus kinase (JAK)–STAT signaling. The anti-inflammatory effect of 15d-PGJ2 in the injured spinal cord appears to be mediated through down-regulation of SOCS1 and suppression of JAK2 phosphorylation [22].

In a rodent model of acute pancreatitis, intraperitoneal administration of 15-PGJ2 significantly reduced the severity of pancreatitis [35]. The STAT3-JAK cascade is an essential inflammatory signaling pathway that mediates the immune responses. Induction of pro-inflammatory cytokines IL-6 and transforming growth factor (TGF)-β1 accompanies human pancreatitis. An intraperitoneal dose (10 mg/kg body weight) of 15d-PGJ2, at which it protects against cerulein-induced pancreatitis, inhibited JAK2-STAT3 activation and reduced serum levels of IL-6 and TGF-β1 in rats [35]. SOCS3 negatively regulates STAT3 activation in models of arthritis, colitis, and intestinal inflammation [80,81].

Cerulein injections induced SOCS3 expression in the pancreas and increased the serum levels of IL-6 and TGF-β1. Treatment with SOCS3 antisense oligonucleotide suppressed the cerulean-induced secretion of IL-6 and TGF-β1. Thus, SOCS3 expression appears to be an adaptive defensive response to pancreatic inflammation [35]. SOCS3 expression was substantially induced by 15d-PGJ2 treatment [35]. These data suggest that SOCS3 may mediate the anti-inflammatory action of 15d-PGJ2 in the experimentally induced rat pancreatitis.

Chronic pancreatitis accounts for part of the pancreatic cancer in humans, and inflammation promotes initiation and progression of pancreatic ductal adnocarcinoma in a mouse model of the disease. Chronic cerulein injections caused a dramatic increase in COX-2 expression in pancreas with histopathological features that resemble human pancreatic ductal adenocarcinoma [82]. In a K-Ras-driven mouse model of pancreatic ductal adenocarcinoma, the inflammatory mediator STAT3 is important in cell proliferation, metaplasia-associated inflammation, and MMP-7 expression during neoplastic development. Furthermore, STAT3 signaling enforces MMP-7 expression in pancreatic ductal adenocarcinoma cells and that MMP-7 deletion limits the tumor size and metastasis in mice. The serum MMP-7 level in human patients with pancreatic ductal adenocarcinoma correlated with metastatic disease and survival. Therefore, STAT3 and MMP-7 may contribute to the pathogenesis of pancreatic ductal adenocarcinoma [83].

5.2.2. Cell culture studies

Rat pancreatic acinar AR42J cells treated with cerulein exhibited elevated mRNA expression of IL-6 and TGF-β. The cerulein-induced upregulation of the pro-inflammatory cytokines was abrogated by blocking the expression of SOCS3, a negative regulator of JAK-STAT3 signaling, using antisense oligonucleotide. 15d-PGJ2 restored SOCS3 expression and thereby inhibited the activation of the JAK2-STAT3 inflammatory signal transduction pathway and concomitant cytokine expression in pancreatic acinar cells challenged with ceruline [35].

The cyclin-dependent kinase inhibitor $p21^{WAF1}$ is expressed in most, if not all, differentiated cells in the human body and represents an important regulator of cell cycle control and terminal differentiation in the monocyte/macrophage lineage. IL-13 upregulated $p21^{WAF1}$ expression in human blood monocytes via the JAK/STAT signaling pathway [84].

15d-PGJ2 reduced the phosphorylation of STAT1 and STAT3 as well as JAK1 and JAK2 in activated astrocytes and microglia. This led to the suppression of JAK–STAT-dependent inflammatory responses. 15d-PGJ2 rapidly induced the SOCS 1 and 3, which in turn inhibited JAK activity in activated glial cells [85].

Treatment of cultured CD133 positive-brain tumor stem cells with 15d-PGJ2 resulted in a reversible inhibition of gliosphere formation. 15d-PGJ2 inhibited the proliferation and expansion of glioma and gliosphere cells and also induced cell cycle arrest and apoptosis in association with the inhibition of epidermal growth factor (EGF)/basic fibroblast growth factor-induced suppression of the JAK-STAT3 pathway in gliosphere cells [86].

Treatment of human oral squamous cell carcinoma cells with 15d-PGJ2-induced apoptosis, which was accompanied by down-regulation of the oncogenic STAT3 signaling. Inhibition of STAT3 by 15d-PGJ2 was abolished by exogenous stimulation with TGF-β, but not IL-6. 15d-PGJ2 selectively abrogated constitutive and IL-6-induced JAK phosphorylation without affecting EGF receptor-activated levels. Moreover, the inhibitory effect of 15d-PGJ2 on JAK signaling required the reactive α,β-unsaturated carbon within the cyclopentenone ring. JAK inhibition and suppression of EGF receptor-independent STAT3 activation by 15d-PGJ2 represent a promising approach for induction of apoptosis in human oral squamous cell carcinoma cells [87].

Embryonic stem (ES) cells are genetically normal, pluripotent cells, capable of self-renewal and differentiation into all cell lineages. Leukemia inhibitory factor (LIF) maintains pluripotency in mouse ES cells. 15d-PGJ2 treatment of mouse ES cells inhibited their proliferation and self-renewal. 15d-PGJ2 also attenuated LIF-induced phosphorylation of JAK1 and STAT3 in these cells [88]. Similarly, 15d-PGJ2 inhibited LIF-induced growth and self-renewal of mouse ES cells by blocking the STAT3 pathway [89].

5.3. Activation of Nrf2 signaling

Another important transcription factor modulated by 15d-PGJ2 is Nrf2 that plays an essential role in physiologically important defensive signaling pathways responsible for cellular protection against endogenous and exogenous stresses [90]. The primary function of Nrf2 is to protect cells and organisms from oxidative stress by upregulating the *de novo* synthesis of diverse antioxidant enzymes, such as HO-1, NAD(P)H:quinone oxidoreductase-1 (NQO1), those involved in GSH metabolism and thioredoxin. Nrf2 also plays a role in facilitating the elimination of some electrophilic toxicants by inducing the expression of phase-2 detoxifying enzymes. Recently, the list of stress response and cytoprotective proteins whose expression is primarily regulated by Nrf2 has been expanding, and it is noticeable that many of them have anti-inflammatory functions. Thus, Nrf2 is now recognized as an important therapeutic and preventive target for the management of inflammation-associated disorders [91,92]. Activated macrophages express high levels of Nrf2. By exploiting carrageenan-induced pleurisy as a murine model system for acute inflammation, the role of Nrf2 in anti-inflammatory response has been examined. In Nrf2-deficient mice, tissue invasion by neutrophils persisted during carrageenan-induced inflammation and the recruitment of macrophages was delayed. Treatment of primary cultures of mouse peritoneal macrophages with 15d-PGJ2 activated Nrf2, resulting in an Nrf2-dependent induction of HO-1 and peroxiredoxin I gene expression. Such induction was not observed in macrophages derived from $nrf2^{-/-}$ mice. 15d-PGJ2 and PGA1, but not PGE2, induced the nuclear accumulation of Nrf2. These results demonstrate that Nrf2 regulates the inflammation process downstream of 15d-PGJ2 by orchestrating the recruitment of inflammatory cells and regulating the anti-inflammatory gene expression within those cells [43].

Under physiologic conditions, Nrf2 is normally sequestered in the cytoplasm as an inactive complex with the repressor Kelch-like erythroid cell-derived protein with 'capn'collar homology associated protein (Keap1). The release of Nrf2 from its repressor and subsequent nuclear translocation are most likely to be achieved by alterations in the structure of Keap1. Nrf2, once migrated to nucleus, forms a heterodimer with another protein, such as small Maf, which in turn binds to the antioxidant response elements (ARE) or more correctly electrophile response elements (EpRE), located in the promoter region of genes encoding various antioxidant and phase-2 detoxifying enzymes. As 15d-PGJ2, has an electrophilic α,β-unsaturated carbonyl group in the

cyclopentane ring, this renders the molecule capable of forming a Michael adduct with Keap1, through covalent modification, facilitating the dissociation of Nrf2 from Keap1 for nuclear translocation and subsequently upregulation of genes encoding antioxidant, anti-inflammatory and other cytoprotective proteins. To elucidate whether 15d-PGJ2, as a Michael reaction acceptor, could bind directly to Keap1, biotin-tagged 15d-PGJ2 was treated to rat hepatocyte cell line (RL34). A pull-down analysis with avidin beads followed by probing with anti-Keap1 antibody demonstrated the covalent interaction between 15d-PGJ2 and Keap1 [43,93].

15d-PGJ2 has been reported to undergo reductive metabolism by NADPH-dependent rat alkenal/one oxidoreductase. The major product was found to be 12,13-dihydro-15d-PGJ2, which lacked the ability to induce ARE/EpRE-driven effector gene expression. Induction of NQO1 activity by 15d-PGJ2 was markedly attenuated in mouse embryonic fibroblasts that overexpress rat alkenal/one oxidoreductase [94].

Of the proteins upregulated via the Nrf2 signaling, HO-1 probably plays a most prominent role in cellular defense against inflammatory as well as oxidative insults. 15d-PGJ2 has also been reported to induce HO-1 in various types of cells including glial [95], hepatocytes [96], macrophages [43,97], myocytes [31], lymphocytes [98,99], mesangial cells [100], vascular smooth muscle cells (VSMCs) [101] and pheochromocytoma PC12 cells [102]. 15d-PGJ2 at submicromolar concentrations (0.1–0.5 μM) suppressed the production of TNF-α and NO in LPS-stimulated murine J774 macrophages. Under the same experimental conditions, there was a concomitant induction of HO-1 expression. Inhibition of HO-1 activity or scavenging carbon monoxide (CO), a byproduct derived from HO-1-catalyzed heme degradation, significantly attenuated the observed anti-inflammatory activity of 15d-PGJ2. Furthermore, LPS-induced NF-κB activation, via IκB degradation and p50 nuclear translocation, was diminished in cells subjected to prolonged treatment with the low concentration of 15d-PGJ2. Likewise, a HO inhibitor and a CO scavenger were effective in abolishing the inhibitory effects of 15d-PGJ2 on NF-κB activation induced by LPS. Collectively, these data suggest that even at submicromolar concentrations 15d-PGJ2 can exert an anti-inflammatory effect in macrophages through a mechanism that involves the action of HO-1 in addition to inhibition of IKK through direct interaction [97]. The 15d-PGJ2-induced HO-1 expression has been found to be mediated through activation of Nrf2-Keap1 signaling [99,102].

HO-1 and several other antioxidant enzymes or cytoprotective proteins induced by 15d-PGJ2 is, in large part, regulated by its direct modification of Keap1 to form a covalently bound adduct and the subsequent activation of the ARE/EpRE. It is speculated that constant generation of very low concentrations of 15d-PGJ2 can lead to induction of HO-1 [93].

The mitochondrial-targeted thiol-reactive compound (4-iodobutyl)triphenylphosphonium prevented the 15d-PGJ2-induced upregulation of HO-1 mRNA and protein expression. Furthermore, (4-iodobutyl)triphenylphosphonium prevented the nuclear accumulation of Nrf2, suggesting cross-talk between mitochondria and antioxidant response signal transduction [103].

When treated to rat VSMCs, 15d-PGJ2 significantly induced production of ROS and HO-1 expression. The ROS scavenger NAC or the iNOS inhibitor L-NAME suppressed 15d-PGJ2-induced HO-1 expression. Furthermore, pretreatment with the p38 MAPK inhibitor SB203580 abolished 15d-PGJ2-induced HO-1 expression, while inhibitors of other kinases, such as ERK, JNK, and phosphoinositide 3-kinase, were not effective. Pharmacologic inhibition of p38 MAPK also attenuated Nrf2 translocation into nucleus. The thiol reducing agent dithiothreitol also abrogated 15d-PGJ2-induced nuclear translocation of Nrf2 [101].

Exposure of PC12 cells to the peroxynitrite donor 3-morpholinosydnonimine hydrochloride (SIN-1) induced apoptosis, which accompanied depletion of GSH, JNK activation, mitochondrial membrane depolarization, the cleavage of poly(ADP-ribose)polymerase, and DNA fragmentation. During SIN-1-induced apoptotic cell death, there was an elevated expression of COX-2 which coinsided with 15d-PGJ2 production. Preincubation with 15d-PGJ2 rendered PC12 cells resistant to nitrosative stress induced by SIN-1. 15d-PGJ2 fortified an intracellular GSH pool through upregulation of glutamate cysteine ligase (GCL) [104]. 15d-PGJ2 at sublethal concentrations significantly increased the cellular GSH in cultured PC12 cells by inducing the activity of GCL, the rate-limiting enzyme in the GSH synthesis. Depletion of cellular GSH by BSO completely abolished the adaptive response. 15d-PGJ2 treatment significantly increased the expression of GCL through activation of Nrf2 [105].

The expression of several Nrf2-regulated genes was found to be upregulated in human aortic endothelial cells exposed to laminar shear stress. The critical contribution of Nrf2 to the expression induced by L-flow was ascertained in siRNA-mediated knock down experiments. COX-2 specific inhibitors attenuated Nrf2 nuclear accumulation in the acute phase of lamina flow exposure. 15d-PGJ2 activated the Nrf2 regulatory pathway in human aortic endothelial cells through binding to the cysteines of Keap1. These results demonstrate that 15d-PGJ2 is essential for laminar flow to activate Nrf2 and induce anti-atherosclerotic gene expression [106].

Acute lung injury is a disease process that is characterized by diffuse inflammation in the lung parenchyma. Carrageenan-induced acute lung injury was markedly exacerbated in Nrf2-knockout mice, compared with wild-type mice. Analysis of bronchoalveolar lavage fluids also revealed that the magnitude and the duration of acute inflammation, indicated by albumin concentration and the number of neutrophils, were significantly enhanced in Nrf2-knockout mice. In the lungs of NS-398-treated wild-type mice, the induction of Nrf2 target antioxidant genes as well as the level of 15d-PGJ2 was significantly reduced. Exogenous administration of 15d-PGJ2 reversed the exacerbating effects of NS-398 with the induction of antioxidant genes. Collectively, these results indicate that 15d-PGJ2 has a protective role against acute lung injury by exploiting the Nrf2-mediated transcriptional pathway [27].

15d-PGJ2 also induced GSH *S*-transferase A2, which was associated with Nrf2 and C/EBPβ activation [107].

5.4. Miscellaneous

COX-2 was induced in cultured rat mesangial cells challenged with pro-inflammatory cytokines. 15d-PGJ2 significantly suppressed IL-1β-induced COX-2 expression and PGE2 production. 15d-PGJ2 inhibited the IL-1β-induced increase in binding activities of nuclear proteins to consensus AP-1 site and AP-1-like site of COX-2 promoter but not of NF-κB. IL-1β was unable to activate the COX-2 promoter when the AP-1-like site was mutated. These data suggest that 15d-PGJ2 inhibits IL-1β-induced COX-2 expression by suppression of AP-1 activation in mesangial cells [108].

15d-PGJ2 was found to bind to the cysteine 264 of translational inhibition factor eIF4A, thereby blocking the interaction between eIF4A and eIF4G, a key event essential for translation of many mRNAs. Inhibition of translation by 15d-PGJ2 results in increased formation of stress granules, into which TRAF2 is sequestered. Such sequestration of TRAF2 may contribute to the anti-inflammatory activity of 15d-PGJ2, indicative of a novel cross-talk between translation and inflammatory response [109].

5.5. Epigenetic regulation

The ability of 15d-PGJ2 to inhibit TNF-α gene expression through mechanisms that involve histone modification was

investigated. Pretreatment with 15d-PGJ2 (10 μM) inhibited LPS-stimulated TNF-α mRNA expression and TNF-α promoter activity in THP-1 monocytes or phorbol ester-differentiated cells to nearly basal levels. Inhibition of HDACs with trichostatin A or overexpression of the HAT CBP could overcome 15d-PGJ2-mediated repression of the TNF-α transcription, indicative of a novel epigenetic mechanism whereby 15d-PGJ2 suppresses cytokine production through factors that regulate histone modifications. LPS stimulation induced an increase in histone H3 and H4 acetylation at the TNF-α promoter, which was reduced by 15d-PGJ2 pretreatment [110].

15d-PGJ2, has been reported to inhibit the expression of a number of genes involved in the pathogenesis of arthritis. However, its effects on COX-2 remain controversial. In human synovial fibroblasts, IL-1β-induced expression of COX-2 protein and its mRNA transcript and COX-2 promoter activity were inhibited by 15d-PGJ2. IL-1β-induced histone H3 acetylation was selectively blocked by 15d-PGJ2. The reduction of histone H3 acetylation did not correlate with the recruitment of HDACs to the COX-2 promoter. Also, treatment with the specific HDAC inhibitor, trichostatin A, failed to relieve the suppressive effect of 15d-PGJ2, indicating that HDACs are not involved in the inhibitory effect of 15d-PGJ2. Furthermore, 15d-PGJ2 blocked IL-1β-induced recruitment of p300 to the COX-2 promoter, which may explain decreased histone H3 acetylation and COX-2 expression. In accordance with this, overexpression of p300, but not of a mutant p300 lacking HAT activity, relieved the inhibitory effect of 15d-PGJ2 on COX-2 promoter activation. These data suggest that 15d-PGJ2 can inhibit IL-1β-induced COX-2 expression by an HDAC-independent mechanism, probably by interfering with HAT p300 [46].

6. Role for 15d-PGJ2 in pro-resolving signal response

The termination of once-initiated immunologic and inflammatory responses represents a pivotal mechanism responsible for the control of inflammation. Recent studies demonstrated that COX-2 induced at the late phase of inflammation aids in the switching off inflammatory response by generating 15d-PGJ2. 15d-PGJ2 and its precursor PGD2 are synthesized by COX-2 in the inflamed tissues, and may participate in the resolution of inflammation due to their potent anti-inflammatory activitites [56]. In animal models, expression of PGD2 synthase declines during acute inflammation, only to rise again in the resolution phase, corroborating the possible role of PGD2 and its dehydration product 15d-PGJ2 in resolving inflammation. Their production results in transcriptional regulation of a distinct set of genes, which leads to the inhibition of cytokine secretion and other essential immunologic and inflammatory events mediated by antigen-presenting cells like dendritic cells or macrophages. These prostaglandins also can affect the priming and effector functions of T lymphocytes and induce their apoptotic cell death [66].

15d-PGJ2 was detected in a self-resolving peritonitis. Together with PGD2, 15d-PGJ2 controls the balance of pro- vs. anti-inflammatory cytokines that regulate leukocyte influx and monocyte-derived macrophage efflux from the inflamed peritoneal cavity to draining lymph nodes leading to resolution. Specifically, inflammation in hematopoietic PGD2 synthase knockout mice was more severe during the onset phase arising from a substantial cytokine imbalance, resulting in enhanced polymorphonuclear leukocyte and monocyte trafficking [111].

Failure in resolving acute inflammation leads to persistence of the inflammatory response and may contribute to the development

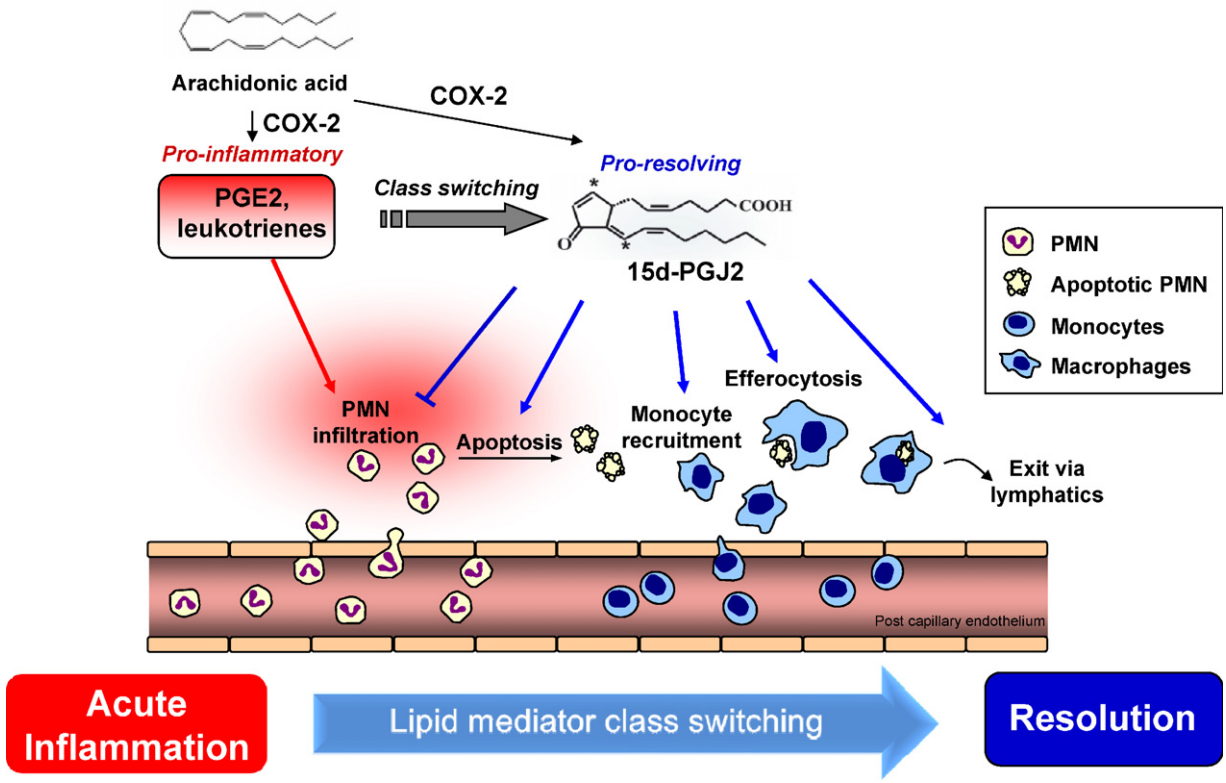

Fig. 3. A proposed scheme illustrating pro-resolving action of 15d-PGJ2. At the beginning of acute inflammation, pro-inflammatory lipid mediators, such as PGE2 and leukotrienes, are generated from arachidonic acid via the COX-2 pathway, which are involved in progression of inflammatory response. These mediators reversely act as inducers of "class switching" redirecting arachidonic acid to pro-resolving prostaglandins. 15d-PGJ2, one of pro-resolving prostaglandins, induces the resolution of inflammation through several putative mechanisms: preventing further infiltration of PMNs; inducing apoptosis of residual PMNs; facilitating non-phlogistic monocyte infiltration; promoting uptake of apoptotic PMNs (efferocytosis); activating exit of macrophages engulfing apoptotic PMNs via lymphatics, etc.

of chronic inflammation. In an acute pleurisy, polymorphonuclear leukocytes (PMNs) were found to predominate at the onset of the lesion but decreased in number by undergoing apoptosis, the principal mechanism by which PMNs died in this model. PMNs were progressively replaced by monocytes, which differentiate into macrophages. As with PMNs, macrophages also underwent programmed cell death or apoptosis, leading to an abatement of the inflammatory response and eventually resolution. Notably, apoptotic death that occurred in both of these inflammatory cell types was mediated by pro-resolving COX-2-derived 15d-PGJ2, which is uniquely expressed during active resolution. These results provide insight into the mechanisms that switch off acute inflammation and prevent complications of wound healing and potentially the development of immune-mediated chronic inflammation [44]. Fig. 3 illustrates the proposed mechanism by which 15d-PGJ2 mediates pro-resolving effects.

7. Stability, bioavailability and the fate of 15d-PGJ2

15d-PGJ2 is chemically reactive due to its electrophilic nature, and a substantial amount (97–99%) of exogenously added 15d-PGJ2 to endothelial cells was found to be inactivated in the medium and hence failed to enter the cells to initiate cell signaling [93]. In the physiological system, this reactive cyclopentenone prostaglandin may be carried by some plasma protein, such as albumin, and thereby stabilized during circulation. Albumin carries with it a heavy load of fatty acids, and albumin-bound fatty acids appear to be important mediators of tubular injury in nephrosis [112].

Human serum albumin (HSA), the most abundant protein in plasma, catalyzes the conversion of PGJ2, a dehydration product of PGD2, to yield Δ^{12}-PGJ2. HSA may bind to and stabilize Δ^{12}-PGJ2 in a serum. A molecular interaction analysis suggested the specific binding of Δ^{12}-PGJ2 binding to HSA at the histidine residue (His146) [113]. 15d-PGJ2 is formed following dehydration of Δ^{12}-PGJ2 may also interact with HAS in a manner similar to that exerted by its precursor.

The anti-tumor effects of 15d-PGJ2 were found to correlate with tumor uptake of albumin, to which it reversibly binds [114]. 15d-PGJ2 has a very short half-life in cells because of GSH conjugation which has been known as a major metabolic pathway of cyclopentenone prostaglandins [115,116]. Also, it has been reported that 15d-PGJ2 is metabolically inactivated by rat alkenal/one oxidoreductase to 12,13-dihydro-15d-PGJ2 [94].

Although little information is available regarding the *in vivo* stability as well as pharmacokinetics of 15d-PGJ2, it is generally believed that prostaglandins are rapidly eliminated via metabolism in the lung, liver, or plasma as and renal excretion [117]. Moreover, prostaglandins including 15d-PGJ2 are highly bound to albumin which is the most abundant protein in the plasma [114,118]. The high albumin binding and rapid elimination result in a small apparent volume of distribution (V_d), and high total body clearance (CL), respectively. Thus, it seems to be responsible for a very short plasma half-life ($t_{1/2}$) of prostaglandins, based on the principle that the plasma $t_{1/2}$ is proportional to the ratio of V_d/CL [119]. PGE2 (dinoprostone) and prostaglandin I_2 (epoprostenol) have a plasma $t_{1/2}$ of less than 1 and 2–3 min, respectively [120]. However, the plasma $t_{1/2}$ of 15d-PGJ2 is unknown [117].

Mean plasma levels of 15d-PGJ2 in human subjects are highly variable depending on the pathophysiological conditions. The median plasma 15d-PGJ2 level was significantly higher in patients with an acute stroke than that in controls (60.6 pg/mL vs. 5.0 pg/mL) [121]. In this study, levels of 15d-PGJ2 were also found to be significantly elevated in patients with vascular risk factors (history of hypertension and or diabetes) and with atherothrombotic infarcts (113.9 pg/mL) than in those with infarcts of undetermined origin (11.4 pg/mL). Based on these observations, it is likely that that increased plasma 15d-PGJ2 concentrations represent good early and late neurological outcome and smaller infarct volume in atherothrombotic ischemic stroke. These findings suggest a neuroprotective effect of 15d-PGJ2 in atherothrombotic ischemic stroke [121]. However, levels of 15d-PGJ2 are not significantly altered in patients with multiple sclerosis compared with healthy subjects (about 15 ng/mL). Treatment with IFN-β also had no effect on the level of 15d-PGJ2 [122]. Despite its expected poor pharmacokinetics as mentioned above, *in vitro* pharmacological activities of 15d-PGJ2 seem to be preserved in most of the animal disease models studied. Further investigation on the pharmacokinetics, pharmacodynamics, and mechanism of *in vivo* action regarding 15d-PGJ2 is required to clarify this discrepancy.

To date, a few attempts have been made to further improve the *in vivo* efficacy of prostaglandins including 15d-PGJ2 (Table 2). The aqueous solubility of 15d-PGJ2 is quite low (0.003 mg/mL; log $P = 3.98$) as other lipophilic prostaglandins (from human metabolism database; http://www.hmdb.ca/metabolites/HMDB05079). Thus, formulation strategies for a poorly soluble drug, including lipid- or polymer-based emulsions, micelles, liposomes, and nanoparticles, could be feasible for therapeutic application of 15d-PGJ2. Constant intravenous infusion has been often used to prolong systemic exposure of a drug with poor *in vivo* stability. It has been reported that 5-days constant intravenous infusion of PGA1 derivative at a dose of 80 mg/kg inhibited tumor growth in male Wistar rats with subcutaneous Walker256 tumors, but single intravenous bolus injection at the same dose was

Table 2
Efficacy of 15d-PGJ2 in various animal disease models.

Dosing regimen	Animal	Disease	Efficacy	Reference
Single intravenous bolus injection (0.3 mg/kg)	Male Wistar rats	Multiple-organ failure by cell wall fragments from G+ and G− bacteria	Anti-inflammatory	[128]
Single intravenous bolus injection (2 mg/kg)	Female Swiss Webster mice	Acute pancreatitis	Anti-inflammatory	[37]
Single intravenous bolus injection and single intratracheal instillation (0.01–1 mg/kg)	Male ICR mice	Acute lung injury induced by LPS	No effect	[129]
Single intraventricular infusion (50 pg/rat, 10 μL, 2 min)	Male Long-Evans rats	Ischemic brain injury	Anti-inflammatory	[19]
Single intravenous bolus injection (1 mg/kg)	Male Wistar rats	Ischemic acute renal failure	Anti-inflammatory	[130]
Single intraperitoneal bolus injection (0.01–1 mg/kg)	Male Wistar rats	Ischemic gut injury	Anti-inflammatory	[30]
Single intravenous bolus injection (0.3 mg/kg)	Male Sprague–Dawley rats	Ischemic gut injury	Anti-inflammatory	[131]
Multiple intravenous bolus injection (2 mg/kg/day)	Male C57BL/6 mice Male Balb/c mice	Subcutaneous B16 tumors Subcutaneous C26 tumors	Anti-tumor No effect	[114]
Multiple intraperitoneal bolus injection (1 mg/kg/day)	Female athymic nude mice	Subcutaneous A549 or H460 tumors	No effect	[132]
Multiple intraperitoneal bolus injection (0.01–1 mg/kg/day)	Female Lewis rats	Arthritis in tail	Anti-inflammatory	[133]

ineffective [123]. Chemical modifications including the synthesis of long-acting analogue and the conjugation with targeting moiety can be another potential strategy. Long-acting analogues of PGE1 (misoprostol and gemeprost) and F2 (carboprost) are currently marketed, and their half-lives range from 10 to 45 min [124]. Recently, for targeting 15d-PGJ2 to hepatic stellate cells (HSC), the 15d-PGJ2 coupled to two different HSC-selective drug carriers, *i.e.*, human serum albumin modified with the sugar mannose-6-phosphate (M6PHSA) or human serum albumin modified with PDGF-receptor recognizing peptides (pPBHSA), was developed [117]. The two conjugates (15d-PGJ2 + M6PHSA and 15d-PGJ2 + pPBHSA) were specifically taken up by cultured HSC and successfully targeted to HSC in male Wistar rats with liver fibrosis.

8. Conclusions and perspectives

COX-2 plays a role in producing pro-inflammatory prostaglandins, thereby establishing acute inflammation. However, multiple lines of evidence suggest that COX-2 induction also contributes to the resolution phase of inflammation through production of anti-inflammatory15d-PGJ2. This lipid electrophile can directly bind to some proteins and changes their structure and functions. It has been shown that this provokes important biological responses, including protection against inflammatory as well as oxidative stress [93]. For instance, 15d-PGJ2 regulates the synthesis of pro-inflammatory cytokines and proteins by interacting with NF-κB, AP-1, STAT3 and their modulators. Besides down-regulation of pro-inflammatory signaling mediated by the aforementioned transcription factors, 15d-PGJ2 can exert a potent anti-inflammatory effect by stimulating the Nrf2-Keap1 pathway [43]. 15d-PGJ2 treatment often decreases the upregulation of COX-2 expression induced by several inflammatory stimuli, indicative of its involvement in a negative feedback limiting further inflammatory response mediated by COX-2.

However, intracellular localization and protein adducts of reactive lipids have been difficult to detect, and the methods of detection rely largely on antibodies raised against specific lipid-protein adducts. As an alternative approach to monitoring oxidized lipids in viable cells, this electrophilic lipid was tagged with either biotin or the fluorophore BODIPY. Tagged 15d-PGJ2 can now be utilized to monitor its subcellular localization and to assess protein modification generated *in situ* [125].

As locally produced 15d-PGJ2 and its precursor cyclopentenone PGD2 are involved in the regulation of inflammatory responses, they possess therapeutic value in the management of human inflammatory disorders, such as atherosclerosis and rheumatoid arthritis [126]. The possible use of exogenously administered 15d-PGJ2 as a tool to maintain anti-inflammatory balance in this condition deserves special attention. In fact, expression of COX-2 can be up- or down-regulated, depending on the stage of inflammation. In basal conditions (inactivated stage), physiological PGD_2 metabolites such as PGJ2 closes a negative feedback loop on COX-2 expression, whereas in activated stages, such as stress, COX-2 is activated by enhanced levels of PGD2 metabolites, with production of its main product, PGE2. By administering supra-physiological doses of 15d-PGJ2, as we do in stress, one could expect an inhibition in COX-2 expression and PGE2 production, as seen in different models.

Accordingly, exogenous administration of 15d-PGJ2 should exert a more powerful anti-inflammatory effect. Thus, the anti-inflammatory effect of 15d-PGJ2 is more apparent in stressful situations than in resting status, due to induction of endogenous 15d-PGJ2 production, which, when combined with exogenous 15d-PGJ2, could exert a more powerful effect [15]. However, the use of exogenous 15d-PGJ2 is hampered by the large-scale synthesis and purification, specially of isomers, and the instability of this electrophilic lipid as well as its relatively short half-life anticipated. In this context, a synthetic derivative of 15d-PGJ2 with increased stability and bioavailability can be considered.

A novel synthetic cyclopentenone derivative, 3-*tert*-butyldimethylsilyloxy-5-(E)-iso-propylmethylenecyclopent-2-enone (CTC-35) was found to be a potent NF-κB inhibitor with proapoptotic activity in estrogen receptor-negative breast cancer cells. The results open new perspectives in the search for novel synthetic cyclopentenone derivatives effective in the treatment of tumors as well as inflammatory ailments in which NF-κB is aberrantly overactivated [76]. A synthetic 15d-PGJ2 analoague, 13,14-dihydro-15-deoxy-Δ^7-PGA1 methyl ester (TEI-9826), has a unique anti-tumor activity, and lipid microsphere integrated TEI-9826 (Lipo TEI-9826) has been selected for as a promising candidate for clinical trial because of its stability in serum. Lipo TEI-9826 exhibited marked anti-tumor effects in several animal xenograft models. Pharmacokinetic and toxicological studies using rats suggested that continuous infusion is the most suitable administration method for Lipo TEI-9826 [123]. Further research is warranted to develop more stable derivatives of 15d-PGJ2 with sufficient efficacy and proper formulations for their therapeutic applications in diseases in which overactivated inflammatory response plays prominent etiologic and pathogenic roles.

Acknowledgements

This work was supported by the Outstanding Scholar Support grant (no. 341-2008-1-C00025) and the grant (no. 2009-0083533) from the National Research Foundation (NRF) funded by the Korean government (MEST).

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